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Food for thought

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Food for thought: Leptin regulation of hippocampal function and its role in Alzheimer's disease.

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Abstract.

Accumulating evidence indicates that diet and body weight are important factors associated with Alzheimer's disease (AD), with a significant increase in AD risk linked to mid-life obesity, and weight loss frequently occurring in the early stages of AD. This has fuelled interest in the hormone leptin, as it is an important hypothalamic regulator of food intake and body weight, but leptin also markedly influences the functioning of the hippocampus; a key brain region that degenerates in AD. Increasing evidence indicates that leptin has cognitive enhancing properties as it facilitates the cellular events that underlie hippocampal-dependent learning and memory. However, significant reductions in leptin's capacity to regulate hippocampal synaptic function occurs with age and dysfunctions in the leptin system are associated with an increased risk of AD. Moreover, leptin is a potential novel target in AD as leptin treatment has beneficial effects in various models of AD. Here we summarise recent advances in leptin neurobiology with particular focus on regulation of hippocampal synaptic function by leptin and the implications of this for neurodegenerative disorders like AD.

Highlights:

- Leptin displays cognitive enhancing properties at hippocampal excitatory synapses.
- The leptin responsiveness of hippocampal synapses markedly declines with age.
- Impairments in leptin function are linked to the risk of AD.
- Leptin displays cognitive enhancing and neuroprotective actions in AD models.
- The leptin system is a promising target for the treatment of AD.

Key words: Leptin; Alzheimer's disease; hippocampus; excitatory synaptic transmission; AMPA receptor trafficking; synaptic plasticity.

Abbreviations.

AD: Alzheimer's disease

A β : amyloid beta

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

APP: amyloid precursor protein

ATP: adenosine tri-phosphate

BACE 1: β -site amyloid precursor protein cleaving enzyme 1

Bcl-xl: B-cell lymphoma-extra large

BK: Calcium-activated large conductance potassium channel.

CNS: central nervous system

CSF: cerebrospinal fluid

db: diabetes gene

GABA: gamma-aminobutyric acid

JAK: janus kinase

K_{ATP}: ATP-sensitive potassium channel

LTD: long term depression

LTP: long term potentiation

MAP2: Microtubule Associated Protein 2

MAPK: mitogen-activated protein kinase

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NMDA: N-methyl-D-aspartate

ob: obese gene

ObR: leptin receptor

p-STAT3: phosphorylated STAT3

p-tau: phosphorylated tau

PI 3-kinase: phosphoinositide 3-kinase

PI(3,4,5)P₃: Phosphatidylinositol (3,4,5)-trisphosphate

PI(4,5)P₂: Phosphatidylinositol (4,5)-bisphosphate

POMC: proopiomelanocortin

PTEN: Phosphatase and tensin homolog

PTP1B: { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Protein_tyrosine_phosphatase"](http://topics.sciencedirect.com/topics/page/Protein_tyrosine_phosphatase) } 1B

SC: Schaffer collateral

SLM: stratum lacosum-moleculare

SOCS-3: suppressor of { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Cytokines"](http://topics.sciencedirect.com/topics/page/Cytokines) } signaling-3

STAT: signal transducers and activators of transcription

STP: short term potentiation

TA: temporoammonic

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Introduction.

The hormone leptin is the 16kDa protein product of the obese (*ob*) gene (Zhang et al, 1994) and it is primarily, but not exclusively, produced by white adipose tissue. The circulating levels of leptin are proportional to body fat content, with obesity associated with elevated levels of leptin and development of leptin resistance (Maffei et al, 1995; Considine et al, 1996). It is well established that leptin enters the brain via a saturable transport system (Banks et al, 1996), possibly via receptor-mediated transcytosis across the blood brain barrier. This transport process is regulated by many factors including dietary fat (Banks et al,

2004). Leptin may also access the brain via the cerebrospinal fluid (CSF; Schwartz et al, 1996), as the choroid plexus expresses high levels of ObRs and this is the main site of CSF production. Numerous functional and anatomical studies have identified the hypothalamus as a key target for leptin in the CNS, and leptin regulates food intake and body weight via its actions in this brain region (Spiegelman and Flier 2001). However increasing evidence indicates that leptin is a pleiotropic hormone with a diversity of central actions that extend beyond its hypothalamic actions.

Leptin and its receptor.

Positional cloning techniques performed in mice identified that leptin is encoded by the obese (*ob*) gene (Zhang et al, 1994). Leptin is highly homologous amongst different species and its structure is also very similar to other cytokines (Madej et al, 1995). Early studies suggested that adipose tissue was the only site of leptin expression. However, subsequent studies revealed wide spread expression of leptin in peripheral tissues including skeletal muscle and gastric mucosa (Wang et al, 1998) and that external factors, like hypoxia and insulin, markedly influence the peripheral expression of leptin (Mise et al, 1998; Shekhawat et al, 1998).

Leptin has also been detected in the CNS, with high levels of leptin mRNA and leptin immunoreactivity observed in hypothalamic, hippocampal and cortical brain regions (Morash et al, 1999; Ur et al, 2002). The subcellular distribution of leptin varies between different neuronal populations (Hakanssen et al, 1998), as leptin immunolabelling is restricted to the nucleus in hippocampal CA2/CA3 neurons, whereas perinuclear and nuclear expression of leptin is evident in the dentate gyrus (Ur et al, 2002). The expression of leptin protein throughout the brain has fuelled the possibility that local release of leptin occurs from neurons, however this has yet to be demonstrated experimentally.

Leptin produces its biological actions by activating the leptin receptor (ObR), a class I cytokine receptor that is encoded by the diabetes gene (*db*; Tartaglia et al, 1995). Six isoforms of ObR have been identified (ObRa-f) that are generated by alternate splicing of the *db* gene (Lee et al, 1996; Wang et al, 1998). These isoforms consist of an extracellular ligand binding domain that is analogous across all isoforms, and an intracellular domain that varies in length between isoforms. With the exception of ObRe, which lacks a membrane spanning region, the isoforms can be subdivided into short and long forms (Lee et al, 1996). The short

isoforms (ObRa,c,d &f) typically have a short intracellular domain consisting of 30-40 residues, whereas the intracellular region of the long isoform, ObRb, comprises 302 residues and includes specific motifs required for activation of downstream signalling cascades (Lee et al, 1997). ObRb has been identified as the main signalling competent form of the receptor (Fig 1). However the prime role of the short isoforms is in regulating the internalisation and degradation of leptin (Uotani et al, 1999). As ObRe is the major binding site for leptin in the plasma, it is thought to be involved in buffering the plasma levels of leptin.

Leptin receptor expression in the CNS

In accordance with its established role in regulating food intake and body weight, ObRs are highly expressed in hypothalamic nuclei involved in energy homeostasis (Hakansson et al, 1998; Elmquist et al, 1998). High levels of ObR positive immuno-labelling and ObRb mRNA are also evident in many extra-hypothalamic brain regions including the hippocampus, cerebellum, brain stem and thalamus (Hakansson et al, 1998; Elmquist et al, 1998; Shanley et al, 2002; Udagawa et al, 2000). ObR expression in the brain can be regulated by many factors including exercise (Uysal et al, 2017), fasting (https://www.ncbi.nlm.nih.gov/pubmed/?term=Lin%20S%5BAuthor%5D&cauthor=true&cauthor_uid=9427338) and https://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20XF%5BAuthor%5D&cauthor=true&cauthor_uid=9427338}, 1997) and a high fat diet (Koros et al, 2009).

The sub-cellular localisation of ObRs has been characterised in some neuronal systems. Dual-labelling studies performed in cultured cerebellar granule cells (Irving et al, 2006) observed ObRs expression at somato-dendritic regions as ObR positive labelling co-localised with the somato-dendritic marker, MAP2. However, axonal expression of ObRs is also apparent in cerebellar granule cells as ObR immunostaining was also detected on MAP2-negative processes (Irving et al, 2006). High levels of cerebellar ObRs are localised to synapses as punctate ObR immunolabelling that co-localised with specific synaptic markers has been reported (Irving et al, 2006). Likewise, ObRs are highly expressed at somato-dendritic regions and also at points of synaptic contact in hippocampal neurons (Shanley et al, 2002).

Neuronal leptin receptor signalling

The signalling pathways activated by ObRs display parallels to those activated by other members of the class I cytokine receptor family. Following leptin binding, JAK2 is activated resulting in phosphorylation of JAK2 as well as specific tyrosine residues within the C-

terminal domain of ObR. This in turn enables recruitment of various pathways downstream including the STAT (signal transducers and activators of transcription) transcription factors, Ras-MAPK (mitogen-activated protein kinase) and PI 3-kinase (phosphoinositide 3-kinase; Fig 1). In addition, ObR-driven signalling is curtailed by activation of SOCS-3 (suppressor of cytokine signaling) and PTP1B (protein tyrosine phosphatase 1B), which act to suppress ObR signalling by binding to phosphorylated residues on JAK2 (Bjorbaek et al, 2000; Zabolotny et al, 2002).

In the hypothalamus, activation of these leptin-dependent signalling pathways are linked to the ability of leptin to regulate energy balance. Indeed, ObR activation stimulates STAT3 activity in proopiomelanocortin (POMC)-expressing hypothalamic neurons (Vaisse et al, 1996; Ernest et al, 2009), and conditional deletion of STAT3 in mice results in obesity and hyperphagia. This suggests that hypothalamic STAT3 signaling is crucial for homeostatic control of energy balance, but also that activation of STAT is required for leptin regulation of food intake and body weight (Gao et al, 2004). Activation of PI 3-kinase signalling is also implicated in leptin regulation of energy homeostasis (Xu et al, 2010). Moreover, hypothalamic deletion of IRS, which is upstream of PI 3-kinase, results in the development of leptin resistance and an obese phenotype in mice (Kubota et al, 2004). This process is thought to involve PI 3-kinase-driven activation of ATP-sensitive potassium (K_{ATP}) channels (Spanswick et al, 1997; Mirshamsi et al, 2004) as leptin-dependent inhibition of glucose-responsive hypothalamic neurons in acute brain slices involves this mechanism. In addition, ObR-driven activation of ERK signalling is thought to be key for the correct development of specific hypothalamic feeding circuits (Bouret et al, 2012).

Many studies have examined the key signalling cascades that are activated by hippocampal and hypothalamic ObRs. Indeed, STAT3 signalling underlies the ability of leptin to promote neurogenesis in the dentate gyrus (Garza et al, 2008), and stimulation of this pathway also contributes to the neuroprotective actions of leptin in hippocampal neurons (Guo et al, 2008; Doherty et al, 2013). Like hypothalamic ObRs, a PI 3-kinase-dependent process couples ObRs to modulation of hippocampal potassium channel function, but unlike the hypothalamus, large conductance Ca^{2+} -activated K^{+} (BK) are the downstream target for leptin in hippocampal neurons (Shanley et al, 2002; O'Malley et al, 2005; Gavello et al, 2012). An ERK-dependent process is also implicated in leptin-driven alterations in neuronal morphology, as the leptin-driven increase in dendritic filopodia is blocked by ERK inhibitors

in hippocampal cultures (O'Malley et al, 2007). Furthermore, in the developing hippocampus, the increase in GABAergic synaptic transmission induced by leptin requires activation of the ERK signalling cascade (Guimond et al, 2014).

Leptin regulation of hippocampal synaptic function.

The first indication that leptin influenced hippocampal synaptic function came from studies examining the impact of leptin deficiency and insensitivity on expression of a variety of neuronal markers in *ob/ob* and *db/db* mice (Ahima et al, 1998). Significant reductions in several synaptic proteins, including syntaxin-1 and synaptosomal-associated protein-25, were observed in the hippocampus of *ob/ob* mice; deficits that were normalised by replacing leptin (Ahima et al, 1998). Subsequent immuno-cytochemical studies examining the cellular distribution of ObRs found high levels of ObR expression at points of synaptic contact in hippocampal neurons (Shanley et al, 2002). The main excitatory neurotransmitter within the mammalian brain is glutamate which acts on ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-d-aspartate (NMDA) and kainate receptors or metabotropic glutamate receptors (mGluRs; Rousseaux 2008). ObR expression is also closely associated with synaptically-located GluN2A-containing NMDA receptors, suggesting that NMDA receptors are a possible target for leptin at hippocampal synapses (O'Malley et al, 2007). Indeed, in acute hippocampal slices application of leptin causes facilitation of NMDA receptor mediated synaptic currents, whereas exposure to leptin results in an increase in Ca^{2+} influx via NMDA receptor channels in hippocampal cultures (Shanley et al, 2001). Chronic exposure to leptin during early postnatal development is reported to alter the expression of distinct NMDA receptor subunits in hippocampal tissue (Walker et al, 2007).

Leptin regulates excitatory synaptic transmission at Schaffer collateral (SC)-CA1 synapses

The synaptic activation of NMDA receptors is pivotal for activity-dependent synaptic plasticity evoked at hippocampal SC-CA1 synapses (Bliss and Collingridge, 1993). Numerous studies have demonstrated that hormones, like insulin, modulate activity-dependent hippocampal synaptic plasticity by enhancing NMDA receptor function (McGregor et al, 2015; Fadel et al, 2013). In a similar manner, leptin is reported to enhance NMDA receptor function and this in turn underlies its ability to convert hippocampal short term potentiation (STP) into long-term potentiation (LTP; Shanley et al, 2001). Exposure of acute brain slices to leptin also enhances the magnitude of hippocampal LTP compared to

LTP induced in control conditions (Malekizadeh et al, 2016; Oomura et al, 2006). Treatment with leptin also evokes persistent changes in excitatory synaptic strength that depend on NMDA receptor activation. Indeed, in juvenile hippocampus, leptin has the ability to reverse LTP (depotentialiation) in an NMDA receptor-dependent manner (Moult et al, 2009).

Moreover, at early stages of postnatal development (P5-8) leptin induces a long lasting synaptic depression (LTD) at hippocampal SC-CA1 synapses (Moult and Harvey, 2011) that also requires NMDA receptor activation.

Numerous studies indicate that trafficking of AMPA receptor to synapses underpins activity-dependent LTP at hippocampal SC-CA1 synapses (Collingridge et al, 2004; Herring and Nicoll, 2016). Alterations in the subunit composition of AMPA receptors has been observed following the induction of NMDA receptor-dependent hippocampal LTP (Morita et al, 2014; Plant et al, 2006). AMPA receptor insertion into synapses underlies leptin-induced LTP as the ability of leptin to induce LTP is accompanied by increased rectification of synaptic AMPA receptors (Moult et al, 2010). In addition, application of philanthotoxin, an inhibitor of GluA2-lacking AMPA receptors reversed the effects of leptin, indicating that insertion of GluA2-lacking AMPA receptors underlies the increase in synaptic efficacy induced by leptin (Moult et al, 2010). Consistent with this, the surface expression of GluA1 subunits is elevated following exposure of either cultured hippocampal neurons or acute hippocampal slices to leptin (Moult et al, 2010).

PI 3-kinase activation is pivotal for NMDA-dependent LTP and trafficking of AMPA receptors to hippocampal synapses (Man et al, 2003). Likewise, a PI 3-kinase-dependent process underlies leptin-driven delivery of GluA1 to synapses as an increase in PI(3,4,5)P₃ levels accompanied the synaptic insertion of GluA1 (Moult et al, 2010). However, as PI(3,4,5)P₃ levels are also regulated by the phosphatase PTEN, which reverses the actions of PI 3-kinase by dephosphorylating PI(3,4,5)P₃ into PI(4,5)P₂ (Maehama and Dixon, 1998), leptin-driven inhibition of PTEN could also elevate PI(3,4,5)P₃ levels as observed in hypothalamic neurons (Ning et al, 2009). Indeed, inhibition of PTEN using dominant negative mutants, or pharmacological inhibitors, increased GluA1 surface expression in cultured hippocampal neurons and this effect occluded leptin action (Moult et al, 2010). Inhibition of PTEN in adult hippocampal slices also resulted in a persistent increase in excitatory synaptic transmission that mimicked and occluded leptin-induced LTP (Moult et al, 2010). Thus, in adult hippocampus leptin has potential cognitive enhancing properties as it

induces a novel form of LTP that involves PTEN inhibition and subsequent delivery of GluA1-containing AMPA receptors to synapses.

Leptin and the ageing brain

Ageing is associated with a decline in the functioning of metabolic hormonal systems. It is also clear that metabolic dysfunction is linked to accelerated aging as well as an increased susceptibility to neurodegenerative disease (Stranahan and Mattson, 2011; Kim and Feldman, 2015). Several studies have identified age-dependent alterations in the leptin system in the CNS. Thus, in aged rats, a decrease in leptin responsiveness in hypothalamic neurons is accompanied by lower activation of STAT3 (Scarpace et al, 2000). Decreased uptake of leptin into the hypothalamus is also evident in aged animals; an effect that is accompanied by reduced ObR expression (Fernández-Galaz et al, 2001). In aged animals, the levels of { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Protein_tyrosine_phosphatase"](http://topics.sciencedirect.com/topics/page/Protein_tyrosine_phosphatase) } 1B (PTP1B) and suppressor of { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Cytokines"](http://topics.sciencedirect.com/topics/page/Cytokines) } signaling-3 (SOCS-3) are also diminished, leading to inhibition of ObR-driven signalling ({ [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib26" }; { [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib19" }). Age-related reductions in ObR mRNA have also been detected in a number of extrahypothalamic brain regions including the hippocampus and cortex (Caron et al, 2010), which may contribute to alterations in leptin function with age.

Age-dependent regulation of excitatory synaptic transmission at SC-CA1 synapses by leptin.

In accordance with the high density of ObRs at hippocampal synapses (Shanley et al, 2002; O'Malley et al, 2007), leptin potently modulates excitatory synaptic transmission at hippocampal SC-CA1 synapses. Indeed, rapid but transient synaptic depressions have been observed in juvenile hippocampal slices exposed to leptin (Shanley et al, 2001; Xu et al, 2008; Moulton et al, 2011). However, leptin has completely opposing actions in adult hippocampus, suggesting that the modulatory effects of leptin are age-dependent. In adult (12-16 week old) slices, leptin evokes a persistent increase in excitatory synaptic transmission (leptin-induced LTP) at SC-CA1 synapses (Moulton et al, 2010; Moulton and Harvey, 2011). However the magnitude of leptin-induced LTP is attenuated in aged hippocampus (Moulton and Harvey, 2011), suggesting an age-related decline in leptin-responsiveness.

Several lines of evidence indicate that distinct NMDA receptors are pivotal for different forms of activity-dependent hippocampal synaptic plasticity ([HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/" \l "B28"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/) ; [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/" \l "B4"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/)). The subunit composition and locus of NMDA receptors also varies significantly during postnatal development ([HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/" \l "B35"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586932/)). In accordance with this, the cellular mechanisms underlying the effects of leptin on synaptic function also vary significantly with age and involve molecularly distinct NMDA receptors. Thus, the synaptic depression induced by leptin at early postnatal stages involves GluN2B-containing NMDA receptors whereas leptin-induced LTP in adult hippocampal slices requires activation of GluN2A-containing NMDA receptors (Moult and Harvey, 2011). Divergent signalling are also implicated in the bidirectional effects of leptin on excitatory synaptic transmission as PI 3-kinase mediates leptin-induced LTP in adult hippocampus, whereas ERK signalling is pivotal for synaptic depressions evoked by leptin during early postnatal development (Moult et al, 2011). Overall these findings suggest that the distinct age-dependent effects of leptin involve ObR coupling to different NMDA receptors via activation of divergent signalling pathways.

Leptin also regulates excitatory synaptic transmission at hippocampal TA-CA1 synapses.

Hippocampal CA1 pyramidal neurons are innervated by two distinct glutamatergic inputs that have divergent roles in hippocampal-dependent learning and memory. In addition to the classical tri-synaptic pathway, there is direct innervation of distal dendrites of CA1 neurons within stratum lacunosum-moleculare (SLM) by the temporammonic (TA) input which originates in the layer III of the entorhinal cortex. Recent studies indicate that excitatory synaptic transmission at TA-CA1 synapses is also regulated by the hormone leptin (Luo et al, 2015) and that the regulatory actions of leptin at TA-CA1 synapses are completely distinct from those at SC-CA1 synapses. Application of leptin to juvenile (P11-18) hippocampal slices causes a concentration-dependent increase in excitatory synaptic transmission at TA-CA1 synapses (Luo et al, 2015). At high concentrations of leptin, a persistent increase in synaptic strength (leptin-induced LTP) is evident that involves a postsynaptic expression mechanism and requires activation of NMDA receptors (Luo et al, 2015). Moreover, molecularly distinct NMDA receptors also underlie the effects of leptin on synaptic efficacy at hippocampal TA-CA1 synapses, as GluN2B-, but not GluN2A-, containing NMDA

receptors are implicated in leptin-induced LTP at this synapse (Luo et al, 2015). Previous studies have shown leptin driven activation of PI 3-kinase mediates the effects of leptin on synaptic efficacy at SC-CA1 synapses (Shanley et al, 2001; Moulton and Harvey, 2011; Moulton et al, 2010). Similarly, leptin-induced LTP at TA-CA1 synapses involves activation of PI 3-kinase, but not ERK, signalling (Luo et al, 2015). Insertion of GluA2-lacking AMPA receptors into synapses underlies leptin-induced LTP at TA-CA1 synapses as philanthotoxin prevented the induction of LTP by leptin in hippocampal slices (Luo et al, 2015). Leptin-induced LTP displays parallels to activity-dependent LTP, as HFS-induced LTP at TA-CA1 synapses is also NMDA receptor dependent and expressed postsynaptically (Luo et al, 2015; Remondes and Schumann, 2003). Moreover, leptin-induced LTP occludes activity-dependent LTP at TA-CA1 synapses and vice versa, indicating that the two processes share similar expression mechanisms (Luo et al, 2015).

Behavioural studies indicate a role for TA-CA1 synapses in memory consolidation and the regulation of place cell firing (Remondes and Schuman, 2002; Brun et al, 2002), which contrasts with the role of SC-CA1 synapses in spatial learning and memory (Bliss and Collingridge, 1993; Morris, 1990). The TA input is also implicated in episodic memory processes as this pathway has been shown to integrate cortical and place cell information (Stokes et al, 2015). Recent evidence indicates that leptin regulates episodic-like memory, as leptin improves performance in object-place-context recognition tasks that model human episodic memory (Malekizadeh et al, 2017). Thus, as leptin potentially regulate synaptic efficacy at TA-CA1 synapses, it is feasible that the modulatory actions of leptin at TA-CA1 synapses play a prominent role in influencing not only memory consolidation and place cell activity, but also episodic memory.

Leptin and Alzheimer's disease

AD is a progressive neurodegenerative disorder and the incidence of AD is increasing as people are living longer. Age is a significant risk factor for AD, however diet and lifestyle also greatly influence the likelihood of developing AD later in life. Indeed, individuals with mid-life obesity have a greater risk of AD compared to those of normal body weight (Hassing et al. { [HYPERLINK "http://link.springer.com/article/10.1007%2Fs10571-015-0282-7"](http://link.springer.com/article/10.1007%2Fs10571-015-0282-7) \l "CR51" \o "View reference" }; Xu et al. { [HYPERLINK "http://link.springer.com/article/10.1007%2Fs10571-015-0282-7"](http://link.springer.com/article/10.1007%2Fs10571-015-0282-7) \l "CR134" \o "View reference" }), but the mechanisms responsible for this increased risk are not entirely clear. It is known that the circulating leptin levels correlate

with body fat content and that obesity is associated with high circulating leptin levels and subsequent development of resistance to leptin. Thus dysfunctions in the leptin system may play a role in linking obesity to AD. In support of this, clinical studies have identified marked reductions in circulating leptin levels in AD patients (Power et al, 2001; Holden et al, 2009; Littlejohns et al, 2015). Moreover, an increased risk of developing AD is associated with low body weight and low leptin levels later in life (Power et al, 2013; Hughes et al, 2009). In rodent models of AD, reductions in the circulating levels of leptin have been observed (Fewlass et al 2004), which further supports a correlation between leptin levels and neurodegeneration. In contrast, however several studies have found no link between plasma leptin levels and the risk of AD in humans (Oania and McEvoy, 2015; Teunissen et al, 2015). However monitoring the peripheral circulating levels of leptin may not adequately reflect the CNS levels of leptin and thus the correlative risk of AD. In this respect, downregulation of blood brain barrier-mediated transport of leptin has been linked to AD. Indeed, recent studies indicate not only that leptin binding to megalin at the choroid plexus is involved in the transport of leptin into the brain, but also that megalin expression is downregulated in AD and this correlates with reduced leptin entry into the brain (Dietrich et al, 2008). Moreover, studies examining the CSF levels of leptin in AD patients have identified both increased or unchanged leptin levels (Bonda et al, 2014; Maioli et al, 2015), suggesting possible development of leptin resistance, although this has yet to be verified in functional studies. Nevertheless, it has been established that leptin receptor expression is significantly altered in AD as reductions in ObR mRNA and leptin receptor positive-immunoreactivity has been detected in the hippocampus in post-mortem AD tissue (Bonda et al, 2014; Maioli et al, 2015) and in rodent models of AD (Maioli et al, 2015). Correlated decreases in the levels of ObR and phosphorylated STAT3 (p-STAT3), a key component of ObR signalling, have been detected in post-mortem studies which has also fuelled the possibility that leptin resistance develops during AD (Maioli et al, 2015). However, as the JAK-STAT pathway is activated by all cytokine receptors (Ihle, 1996), the possibility that the attenuated p-STAT3 levels in AD tissue may be unrelated to the leptin system cannot be excluded. Overall, these findings indicate that significant alterations in the leptin system occurs in AD, and as a consequence this has fuelled the possibility that boosting the central actions of leptin may be a novel therapeutic approach in the treatment of AD.

Neuroprotective actions of leptin

Early studies suggested a neuroprotective role for leptin as brain weight is significantly lower in *ob/ob* mice compared to wildtype littermates suggesting that neuronal survival rate is reduced in leptin-deficient animals (Ahima et al, 1999). However, there is now substantial evidence that leptin has powerful protective actions in the brain (Signore et al, 2008). Several studies have since shown that leptin promotes survival of both central and peripheral neurons after exposure to various toxic stimuli, including lack of trophic support, Fe²⁺ ions and elevated glutamate levels (Guo et al, 2008; Doherty et al, 2008; Dicou et al, 2001). Leptin also has beneficial effects in various CNS-driven diseases linked to neuronal cell death. Thus, leptin protects against cerebral ischaemic injury as it reduces the infarct volume and brain oedema following a period of transient ischaemia in mice (Zhang et al, 2013). In models of Parkinson's disease, treatment with leptin protects against { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Dopaminergic"](http://topics.sciencedirect.com/topics/page/Dopaminergic) } neuron death induced by toxic 6-OH dopamine ({ [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib6" }, { [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib41" }) or the mitochondrial toxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Lu et al, 2006).

The three main signalling pathways activated by neuronal ObRs are all implicated in the protective actions of leptin. Thus, activation of PI3-kinase ({ [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib6" }), { [HYPERLINK "http://topics.sciencedirect.com/topics/page/Mitogen-activated_protein_kinase"](http://topics.sciencedirect.com/topics/page/Mitogen-activated_protein_kinase) } ({ [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib41" }) and { [HYPERLINK "http://topics.sciencedirect.com/topics/page/STAT3"](http://topics.sciencedirect.com/topics/page/STAT3) } ({ [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib12" }) mediate leptin-dependent protection of trigeminal sensory, dopaminergic and hippocampal neurons, respectively. Activation of STAT3 is also reported to play a key role in leptin protection against A β -induced toxicity in cortical neurons (Doherty et al, 2013). Although the precise mechanisms underlying the neuroprotective actions of leptin remain to be determined, it is feasible that reducing production of toxic reactive oxygen species, stabilising mitochondrial function and increasing production of the anti-apoptotic protein B-cell lymphoma-extra large (Bcl-xL) are involved (Davis et al, 2014; { [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0197458012004253"](http://www.sciencedirect.com/science/article/pii/S0197458012004253) \l "bib12" }).

It is well known that accumulation of amyloid beta (A β) and formation of plaques is a key pathological feature of AD, and build-up of A β has been linked to degeneration of

hippocampal and cortical neurons (Selkoe and Hardy, 2016). Indeed, neuronal viability is markedly reduced following treatment of cultured neurons with pathological levels of A β . Increasing evidence indicates that leptin decreases toxic neuronal accumulation of A β by interfering with the production, clearance and degradation of A β (Fewlass et al, 2004; Greco et al, 2011; Marwarha et al, 2010; Niedowicz et al, 2013; Fig 2). In neuronal cells, treatment with leptin attenuates A β levels by reducing the activity of β -secretase (Fewlass et al, 2004); an effect that involves leptin-driven activation of AMPK (Greco et al, 2011). Leptin also downregulates transcription of presenilin 1, a key component of the γ -secretase complex, resulting in attenuated A β levels in mice (Niedowicz et al, 2013). Moreover, leptin is reported to inhibit A β aggregation in cortical neurons by reducing the expression of gangliosides at the plasma membrane (Yamamoto et al, 2014). Exposure to leptin also protects neurons from either amyloid beta (A β)-induced toxicity or from the toxic actions of Cu²⁺ ions which promotes A β aggregation (Doherty et al, 2013). ICV delivery of the leptin gene to transgenic APP/PS1 mice also reduces neuronal accumulation of A β associated with attenuated BACE1 levels ({ HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=P%C3%A9rez-Gonz%C3%A1lez%20R%5BAuthor%5D&cauthor=true&cauthor_uid=24430238" } et al, 2014). Leptin deficiency also influences brain levels of A β as crossing transgenic mice overexpressing APP with *ob/ob* mice significantly increases the brain amyloid load (Takeda et al, 2010).

Neurofibrillary tangles comprised of hyper phosphorylated tau are also a key hallmark of AD. Several lines of evidence indicate that the levels of phosphorylated tau (p-tau) are also regulated by the hormone leptin. Indeed, exposure to leptin restricts tau accumulation in neurons, and it reduces phosphorylation of tau via leptin receptor-driven inhibition of GSK3 β (Greco et al, 2010). In addition, treatment of cortical neurons with leptin causes a significant reduction in the ability of A β to increase p-tau levels (Doherty et al, 2013). Moreover, enhanced neuronal levels of p-tau have been observed in tissue from Zucker *fa/fa* rats and in *ob/ob* and *db/db* mice, indicating that impaired leptin function is associated with elevated expression of AD-linked proteins such as tau (Doherty et al, 2013; Gratuze et al, 2016; El Khoury et al, 2016).

Leptin protects against the acute effects of A β on hippocampal synaptic function.

Acute exposure to A β also promotes impairments in hippocampal synaptic function; alterations that are thought to be analogous to the detrimental changes occurring at synapses

in the early stages of AD. Thus, application of A β blocks the induction of activity-dependent hippocampal LTP (Shankar et al 2008; Jo et al, 2011), whereas the magnitude of LTD induced at CA1 synapses is enhanced after exposure to A β in hippocampal slices (Shankar et al, 2008). A β also disrupts glutamate receptor trafficking processes in hippocampal cultures as A β accelerates AMPA receptor removal from synapses which is likely to contribute to AD-linked synaptic deficits (Liu et al, 2010; Hsieh et al, 2006). Recent evidence indicates that leptin also protects against the acute effects of A β on hippocampal synaptic function. Indeed, prior exposure to leptin prevents A β -driven inhibition of LTP at CA1 synapses in acute hippocampal slices (Doherty et al, 2013). Similarly, treatment with leptin reduces the ability of A β to enhance hippocampal LTD and it attenuates A β -driven AMPA receptor endocytosis and removal from synapses (Doherty et al, 2013; Fig 2). ICV administration of leptin also suppresses A β -driven impairments in hippocampal synaptic plasticity and spatial memory in rats in vivo (Tong et al, 2015).

Previous studies have identified that specific fragments of the whole leptin peptide are bioactive, raising the possibility that different parts of the leptin molecule may be CNS active and have the ability to mirror the cognitive enhancing and neuroprotective actions of leptin. Indeed, recent studies have identified that one particular leptin fragment, leptin (116-130) not only enhances the cellular events underlying learning and memory, but it also prevents the aberrant effects of A β on hippocampal synaptic plasticity in acute brain slices and AMPA receptor trafficking in hippocampal neurons (Malekizadeh et al, 2017); effects that parallel the actions of the whole leptin molecule (Doherty et al, 2013). These findings raise the interesting possibility that leptin (116-130) may have therapeutic potential in AD, although this remains to be determined in clinical studies.

Leptin improves hippocampal-dependent memory.

A number of behavioural studies have demonstrated powerful cognitive enhancing properties of leptin as improvements in various hippocampal-dependent memory tasks have been observed following treatment with leptin. Indeed, i.p. administration of leptin significantly improves performance in episodic-like memory (object-place-context recognition) tasks compared to saline-treated mice (Malekizadeh et al, 2017). Likewise, the ability of rats to perform hippocampal-dependent memory tasks in the Morris water maze is also significantly enhanced after peripheral administration of leptin (Oomura et al, 2002). Conversely, dysfunctions in the leptin system are linked to hippocampal memory deficits, as impairments

in spatial memory tasks are evident in leptin-insensitive Zucker *fa/fa* rats and *db/db* mice (Li et al, 2002; Winocur et al, 2005).

Moreover, increasing evidence indicates that leptin also alleviates hippocampal-dependent memory impairments associated with AD. Indeed, leptin treatment improves performance in novel object recognition tasks as well as contextual and cued fear conditioning tasks in 6 month old CRND8 mice that overexpress mutant forms of the human APP gene (Greco et al, 2010). In SAMP8 mice that have elevated levels of A β , treatment with leptin enhances performance in hippocampal-dependent memory tasks (Farr et al, 2006), whereas ICV administration of leptin significantly reduces the impairments in hippocampal-dependent spatial memory that are observed following A β treatment in rats (Tong et al, 2015).

Conclusion

It is now well established that the central actions of leptin extend beyond the hypothalamus and its ability to regulate energy homeostasis. The hippocampus has been identified as a key extra-hypothalamic target for leptin, with increasing evidence revealing important cognitive enhancing and neuroprotective roles for leptin in this brain region. A significant role for leptin in AD pathogenesis is also emerging with numerous studies demonstrating that dysfunctions in the leptin system is linked to an increased likelihood of developing AD later in life. Moreover, leptin is reported to have beneficial effects in various models of AD that replicate the early synaptic deficits and the behavioural and degenerative features of AD. This has led to the possibility that leptin may be a novel potential treatment for use in AD.

Although the therapeutic potential of leptin has not yet been verified in clinical trials, several clinical studies have shown that chronically administered leptin is well tolerated and safe to use in humans (Paz-Filho et al, 2015). However the timing of a leptin-based therapy would be a key factor in determining if leptin has beneficial actions in AD. Targeting the early stages of AD before widespread degeneration of neurons has occurred, is likely to produce the best clinical outcome, but identification of individuals at this stage of AD can be difficult. Leptin-based therapies are more likely to be effective in individuals with low plasma levels of leptin, as leptin replacement therapies have limited effect in individuals with high circulating leptin levels in anti-obesity studies (Bryson, 2000).

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Figure 1. Leptin receptor signalling.

Schematic representation of the key signalling pathways activated downstream of the long form of the receptor, ObRb. Leptin binding to ObRb results in the phosphorylation and activation of JAK2 resulting in phosphorylation of specific tyrosine residues within the C-terminal domain of ObR. This in turn enables recruitment of various signalling pathways that are analogous to those activated by the class I cytokine receptor superfamily. The STAT

(signal transducers and activators of transcription) transcription factors are activated by ObRb resulting ultimately in gene transcriptional changes in the nucleus. The MAPK and PI 3-kinase signalling pathways are also key signalling cascades activated by ObRb.

Figure 2. Leptin protects against diverse actions of A β .

Schematic representation of the key targets for the neuroprotective actions of leptin following activation of ObRs. Proteolytic processing of APP by BACE1, followed by γ secretase results in the generation of toxic A β . Aggregation of A β forms oligomeric A β and ultimately the formation of amyloid plaques. Leptin influences the production and metabolism of A β . Thus, leptin reduces production of A β by attenuating BACE1 activity, whereas the extracellular levels of A β are reduced by leptin as it enhances both the clearance and subsequent degradation of A β . In addition, leptin markedly inhibits assembly of fibrillary forms of A β by reducing expression of GM1 gangliosides. Leptin also prevents to aberrant effects of A β on synaptic function and neuronal viability. Thus, leptin reverses A β -driven removal of AMPA receptors from hippocampal synapses, and it prevents the ability of A β to block the induction of hippocampal LTP induced by HFS. Leptin also has cognitive enhancing properties as it facilitates the cellular events underlying hippocampal LTP. Leptin also has powerful neuroprotective actions as it protects neurons from a variety of toxic stimuli, including A β .